UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., Plaintiffs, -against- SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., Defendants.	Civil Action No. 08 CV 7611 (BSJ)(AJP) ECF Case **DECLARATION OF KAREN L. HAGBERG IN SUPPORT OF DEFENDANTS SANDOZ INC.'S AND MOMENTA PHARMACEUTICALS, INC.'S REPLY IN SUPPORT OF SUPPLEMENTAL CLAIM CONSTRUCTION BRIEF** **EXTERNAL COUNSEL ONLY (FILED UNDER SEAL PURSUANT TO APRIL 10, 2009 PROTECTIVE ORDER)**

I, Karen L. Hagberg, declare:

1. I am a partner with the law firm of Morrison & Foerster LLP, counsel of record for Defendants Sandoz Inc. and Momenta Pharmaceuticals, Inc. ("Sandoz"). I am an attorney duly licensed to practice law in the courts of the State of New York. I make this declaration in support of Sandoz's Reply in Support of its Supplemental Claim Construction Brief. This declaration is based on my personal knowledge, unless otherwise stated, and if called as a witness I could and would testify competently to the facts stated herein.

2. Attached hereto as Exhibit 1 are excerpts of a true and correct copy of the prosecution history of United States patent 5,800,808.

3. Attached hereto as Exhibit 2 are excerpts of a true and correct copy of the prosecution history of United States patent 6,048,898.

4. Attached hereto as Exhibit 3 are excerpts of a true and correct copy of the prosecution history of United States patent 6,342,476.

5. Attached hereto as Exhibit 4 are excerpts of a true and correct copy of the prosecution history of United States patent 6,362,161.

6. Attached hereto as Exhibit 5 are excerpts of a true and correct copy of the transcript of the deposition of Ruth Arnon, Ph.D., taken November 5, 2009.

7. Attached hereto as Exhibit 6 is a true and correct copy of an article titled "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide" Eur. J. Immunol., 1971. pp.242-248, by Dvora Teitelbaum et al., previously submitted as Dckt. 70-6.

8. Attached hereto as Exhibit 7 is a true and correct copy of an excerpt of the prosecution history of application serial number 240,244, marked as exhibit DDX 358 at the May 5, 2010 deposition of Nicole Sampson.

9. Attached hereto as Exhibit 8 are excerpts of a true and correct copy of the Expert Report of Carl Scandella, dated February 3, 2010.

10. Attached hereto as Exhibit 9 are excerpts of a true and correct copy of the Reply Expert Report of Carl Scandella, dated March 19, 2010.

11. Attached hereto as Exhibit 10 is an excerpt of a true and correct copy of a Pharmacia Biotech document titled "Gel filtration Principles and Methods,"

12. Attached hereto as Exhibit 11 are excerpts of a true and correct copy of the Rebuttal Expert Report of Paul L. Dubin, Ph.D., dated March 5, 2010.

I declare under the penalty of perjury that the foregoing is true and correct.

Executed on this third day of December, 2010, in New York, New York.

Karen L. Hagberg

EXHIBIT 1

PATENT
Docket No. 1662/46603

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#5/R
ac 2-4-97

Inventor(s): KONFINO et al.

Serial No.: 08/447,146

Filing Date: May 22, 1995

For: COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

Group Art Unit: 1501

Examiner: Fred Krass

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Henry S. Hadad
Type or print name of person signing certification

Signature 1/22/97 Date

Assistant Commissioner for Patents
Washington D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified patent application as follows:

In the Claims

Please cancel claims 1-16 without prejudice and add the following new claims 17-24:

17. (New) A method of manufacturing copolymer-1 of a desired molecular weight, comprising reacting protected copolymer-1 with hydrobromic acid to form trifluoracetyl copolymer-1, wherein said reaction takes place for a time and at a temperature predetermined by small scale reaction,

treating said trifluoracetyl copolymer-1 with aqueous piperidine solution to form crude

copolymer-1, and

purifying ~~the~~ said ~~crude~~ copolymer-1 to result in ~~pure~~ copolymer-1 of the desired molecular weight.

18. (New) The method of claim 17, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 10-50 hours at a temperature of about 20-28°C.

19. (New) The method of claim 18, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26°C.

20. (New) The method of claim 17, wherein said pure copolymer-1 has a molecular weight of about 5 to 9 kilodaltons.

21. (New) A copolymer-1 of a desired molecular weight, prepared by

reacting protected copolymer-1 with hydrobromic acid to form trifluoracetyl copolymer-1, wherein said reaction takes place for a time and at a temperature predetermined by small scale reaction,

treating said trifluoracetyl copolymer-1 with aqueous piperidine solution to form crude copolymer-1, and

purifying the crude copolymer-1 to result in pure copolymer-1 of the desired molecular weight.

22. (New) The copolymer-1 of claim 21, wherein said protected copolymer-1 is reacted with

hydrobromic acid for about 10-50 hours at a temperature of about 20-28°C.

23. (New) The copolymer-1 of claim 22, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26°C.

24. (New) The copolymer-1 of claim 21, wherein said pure copolymer-1 has a molecular weight of about 5 to about 9 kilodaltons.

Remarks

Further to the teleconference with the Examiner on January 21,1997, applicants respectfully submit new claims 17-24 for consideration. Any inquiry concerning this submission should be directed to the undersigned at the telephone number listed below.

Respectfully submitted,

Dated: 1/22/97

By: _____
Henry S. Hadad (Reg. No. 35,888)

KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

88388-1

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO
08/447,146	05/22/95	KONFINO	E 1662/46603

15M1/0214

KENYON & KENYON
ONE BROADWAY
NEW YORK NY 10004

EXAMINER	
KRASS, F	
ART UNIT	**PAPER NUMBER**
1501	6

DATE MAILED: 02/14/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/447,146	Konfino et al.
Examiner	**Group Art Unit**
FREDERICK KRASS	1501

☒ Responsive to communication(s) filed on *Jan 22, 1997* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *17-24* is/are pending in the application.

Of the above, claim(s) *21-24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *17-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

FREDERICK KRASS
PRIMARY EXAMINER
GROUP 1500

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Restriction Requirement

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I Claims 17-20, drawn to methods for making copolymer-1, classified in class 525, subclass 420 plus.

II. Claims 21-24, drawn to copolymer-1 compositions, classified in class 530, subclass 350 plus.

The inventions are distinct, each from the other because.

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)) In the instant case the product as claimed can be made by another and materially different process, i.e. using recombinant DNA technology.

Because these inventions are distinct for the reasons given above and have acquired separate status in the art due to their recognized divergent subject matter as illustrated by their differing areas of classification restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Hadad on 2-12-97 a provisional election was made with traverse to prosecute the invention of Group I, claims 17-20 Affirmation of this election must be made by applicant in responding to this Office action. Claims 21-24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any

amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1 48(b) and by the fee required under 37 CFR 1.17(h)

New Matter Rejection

Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

The examiner can find no support in the specification for conducting a reaction "predetermined by small scale reaction" as recited in claim 17.

Claim 17, the specification provides no teaching of how to "predetermine" reaction time and temperature by "small scale reaction" No description or example of such "scaling up" appears to be present in the specification as originally filed.

No support can be found for the specific range "5 to 9" in claim 20.

Indefiniteness Rejection

Claims 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The term "desired" in claim 17 is a relative term which renders the claim indefinite The term "desired" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

b) Claim 17, "small scale" is similarly indefinite; there is no recognized point at which a given process begins or stops being "small".

c) Claim 17, the terms "crude" and "pure" are also terms of degree for which the specification provides no guidance and furthermore are somewhat confusing since they are generally not used in the art in relation to polydispersity measurements but rather are reserved to describe the removal of more common impurities, e.g. excess catalyst from a reaction mixture after synthesis is complete.

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made

Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teitlebaum et al (USP 3,849,550).

During patent examination the pending claims are interpreted as broadly as their terms reasonably allow. *In re Zletz*, 13 USPQ 1320. Generally, one does not read into claims in pending applications limitations from the specification. *In re Winkhaus*, 188 USPQ 129; *In re Prater*, 162 USPQ 541. The terms "purifying", "crude" and "pure" in claim 17, interpreted as broadly as their terms reasonably allow, are not limited to removal of particular molecular weight fractions, furthermore, the term "desired" is effectively nonlimiting since if the former terms are construed

to encompass conventional recovery techniques such as filtration then the polymer can be of the same "desired" molecular weight before and after purification.

Patentee teaches the production of copolymer-1 by the known method incorporated by reference at page 3, lines 15 through 30 of the instant specification The reference differs from the instant claims in that it generally describes that method at column 2, lines 53-64 but does not provide an actual example of such synthesis and thus is silent regarding the purification techniques used. It would have been obvious to anyone of ordinary skill in the chemical arts, however, to have recovered the polymer made by that general method using any of a number of well-known recovery/purification techniques such as filtration; this would especially be so for a pharmaceutically/biologically-active product such as copolymer-1 which is intended to be administered to mammals and humans, where impurities are extremely undesirable since they can lead to side-effects and/or interfere with therapy.

The polymers of the prior art are disclosed to have a specified minimum molecular weight of 10,000 (column 1, line 62). As anyone skilled in the polymer art would understand, such molecular weight determinations represent an average of the molecular weights of the species in a given sample, and such sample will comprise species both above and below the specified value. Accordingly, one skilled in the art would have reasonably expected copolymer-1 of the minimum disclosed molecular weight of the prior art to have comprised at least some species within the scope of dependent claim 20.

Correspondence

Any inquiry concerning the substantive issues (i.e. legal and/or technical matters relating to the determination of patentability) of this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (703) 308-4335. The examiner can normally be reached on Monday through Friday from 9:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Bleutge, can be reached on (703) 308-2363. The fax phone number for this Group is (703) 305-5246.

Any inquiry of a clerical nature (missing references, misplaced papers, inaccuracies in mailing, etc) or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-2351.

Frederick Krass
Primary Examiner
Art Unit 1501

File History Report

☐ Paper number _____ is missing from the United States Patent and Trademark Office's original copy of the file history. No additional information is available.

☒ The following page(s) **PTO-892** of paper number **6** is/are missing from the United States Patent and Trademark Office's original copy of the file history. No additional information is available

Additional comments: _____

Form PTO-948 (Rev. 10-93) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 11/477,146

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftspersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 5/22/06 are
A. ___ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
B. X objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a) Acceptable categories of drawings: Black ink. Color.
   - ___ Not black solid lines. Fig(s)___
   - ___ Color drawings are not acceptable until petition is granted. Fig(s)___
2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - ___ Photographs are not acceptable until petition is granted. Fig(s)___
   - ___ Photographs not properly mounted (must use brystol board or photographic double-weight paper). Fig(s)___
   - ___ Poor quality (half-tone) Fig(s)___
3. GRAPHIC FORMS. 37 CFR 1.84 (d)
   - ___ Chemical or mathematical formula not labeled as separate figure. Fig(s)___
   - ___ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis Fig(s)___
   - ___ Individuals waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s)___
4. TYPE OF PAPER. 37 CFR 1.84(c)
   - ___ Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s)___
   - X Erasures, alterations, overwritings, interlineations, cracks, creases, and folds copy machine marks not accepted. Fig(s) 1/2
   - ___ Mylar, velum paper is not acceptable (too thin). Fig(s)___
5. SIZE OF PAPER. 37 CFR 1.84(f) Acceptable sizes:
   - 21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
   - 21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
   - 21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
   - 21.0 cm. by 29.7 cm. (DIN size A4)
   - ___ All drawing sheets not the same size. Sheet(s)___
   - ___ Drawing sheet not an acceptable size. Sheet(s)___
6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

Paper size

21.6 cm X 35.6 cm (8 1/2 X 14 inches)	21.6 cm X 33.1 cm (8 1/2 X 13 inches)	21.6 cm X 27.9 cm (8 1/2 X 11 inches)	21.0 cm X 29.7 cm (DIN Size A4)
T 5.1 cm (2")	2.5 cm (1")	2.5 cm (1")	2.5cm
L 64 cm (1/4")	64 cm (1/4")	64 cm (1/4")	2.5 cm
R 64 cm (1/4")	64 cm (1/4")	64 cm (1/4")	1.5 cm
B 64 cm (1/4")	64 cm (1/4")	64 cm (1/4")	3.0 cm

Margins do not conform to chart above 1/2
Sheet(s)___
Top (T) ___ Left (L) ___ Right (R) ___ Bottom (B)

7. VIEWS. 37 CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   - ___ All views not grouped together. Fig(s)___
   - ___ Views connected by projection lines or lead lines. Fig(s)___
   - Partial views. 37 CFR 1.84(h) 2
   - ___ View and enlarged view not labled separatly or properly Fig(s)___
   - Sectional views. 37 CFR 1.84 (h) 3
   - ___ Hatching not indicated for sectional portions of an object. Fig(s)___
   - ___ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s)___
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - ___ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)___
9. SCALE. 37 CFR 1.84(k)
   - ___ Scale not large enough to show mechanism with crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)___
   - ___ Indication such as "actual size" or scale 1/2" not permitted. Fig(s)___
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
    - X Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s) 1/2
11. SHADING. 37 CFR 1.84(m)
    - ___ Solid black shading areas not permitted. Fig(s)___
    - ___ Shade lines, pale, rough and blurred. Fig(s)___
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
    - X Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s) 1/2
    - ___ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s)___
    - ___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)___
    - ___ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s)___
13. LEAD LINES. 37 CFR 1.84(q)
    - ___ Lead lines cross each other. Fig(s)___
    - ___ Lead lines missing. Fig(s)___
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
    - ___ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s)___
15. NUMBER OF VIEWS. 37 CFR 1.84(u)
    - ___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)___
    - ___ View numbers not preceded by the abbreviation Fig. Fig(s)___
16. CORRECTIONS. 37 CFR 1.84(w)
    - ___ Corrections not made from prior PTO-948. Fig(s)___
17. DESIGN DRAWING. 37 CFR 1.152
    - ___ Surface shading shown not appropriate. Fig(s)___
    - ___ Solid black shading not used for color contrast. Fig(s)___

COMMENTS:

ATTACHMENT TO PAPER NO.___ REVIEWER YJ DATE 12/2/2010

PTO Cor

EAP 08/15/97

PATENT
Docket No. 1662/46603

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): KONFINO et al.	
Serial No.: 08/447,146	Group Art Unit: 1501
Filing Date: May 22, 1995	Examiner: Fred Krass
For: COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

Date 7/14/97 Atty's Reg. # 35,287

Atty's Signature

KENYON & KENYON

Assistant Commissioner for Patents
Washington D.C. 20231

AMENDMENT UNDER 37 C.F.R. § 1.111

This amendment is responsive to the Office Action dated February 14, 1997 in the above-identified application. Applicants have attached a petition for a two month extension of time, thus making a response due on or before July 14, 1997. Applicants hereby petition for any additional extension of time necessary to maintain the pendency of this case, and any required fee should be charged to Deposit Account 11-0600.

Please amend the above-identified application in the following manner:

IN THE CLAIMS:

Please cancel claims 21-24, without prejudice, and amend claim 17 as follows:

Claim 17, line 8, after "purifying", delete "the";

after "said", delete "crude";

after "result in", delete "pure".

REMARKS

Claims 17-20 are all the claims pending in the application. Applicants have cancelled claims 21-24 without prejudice in response to the restriction requirement previously issued on February 12, 1997. Applicants reserve the right to pursue the cancelled subject matter in a continuation application in the future.

As a preliminary matter, Applicants note that the Examiner has not indicated consideration of the Information Disclosure Statement filed October 30, 1995 in parent application 08/447,146. Applicants are resubmitting a copy of this Information Disclosure Statement and attached PTO form 1449 for the convenience of the Examiner. If the Examiner does not have copies of the references cited therein from when they were originally submitted in October 1995, the Examiner should contact the undersigned and these references will be provided immediately.

Applicants turn now to address the rejections set forth in the outstanding Office Action. On page 3 of the Office Action, claims 17-20 are rejected under 35 U.S.C. §112, first paragraph, for lack of written description. In particular, the Examiner states that he can find no

support in the specification for conducting a reaction "predetermined by small scale reaction" nor for the specific pH range "5 to 9" in claim 20. Applicants respectfully direct the Examiner to the specification as originally filed, *e.g.* from page 8, line 29 to page 9, line 9, which provides support for the pending claims. Accordingly, Applicants request that the Examiner withdraw this 35 U.S.C. §112, first paragraph, rejection.

On pages 3-4 of the Office Action, the Examiner rejects claims 17-20 under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner points to the specific terms "desired", "small scale", "crude" and "pure" in claim 17.

With respect to the terms "crude" and "pure", Applicants have editorially amended claim 17 to remove these terms in order to obviate this basis of rejection. Since it is apparent from the claim language that the purifying step of claim 17 provides a purification of crude copolymer-1, the removal of the terms "crude" and "pure" should not substantively alter these claims.

With respect to terms "desired" and "small scale", Applicants respectfully traverse this rejection on the basis that one of ordinary skill in the art would understand the scope of these terms in view of the disclosure in the specification. The term "desired" in the phrase "desired molecular weight" is readily understandable to one of ordinary skill in the art; *i.e.*, that the presently claimed method allows one to choose and obtain a particular molecular weight fraction of copolymer-1. The metes and bounds of the term "small-scale" are similarly understandable to one of ordinary skill in the art. The specification at pages 8-9 teaches the use of test reactions over an extended time period at a particular temperature to assess the exact parameters which provide copolymer-1 of a particular molecular weight fraction; *e.g.*, 17 hours at 26°C to provide

copolymer-1 having a molecular weight fraction of 5 to 9 kDa. This assessment allows individuals of ordinary skill in the art to perform larger scale reactions and obtain large volumes of copolymer-1 of a desired molecular weight. Since the metes and bounds of claim 17 would be clear to one of ordinary skill in the art, Applicants respectfully request withdrawal of this indefiniteness rejection.

On pages 4-5 of the Office Action, the Examiner rejects claims 17-20 as being obvious over Teitelbaum, et al. Applicants respectfully traverse this rejection, and submit that the presently claimed method is neither taught nor suggested by the cited reference for the following reasons.

As described above, the presently claimed method is directed to pre-determining by small scale reaction the time and temperature of the reaction of protected copolymer-1 with hydroblomic acid to form trifluoracetyl copolymer-1. This reaction allows for the production of copolymer-1 of the desired molecular weight fraction. In contrast to a mere purification, the presently claimed method allows for the precise fractionation of copolymer-1 to produce a particular molecular weight range of copolymer-1, *e.g.*, 5 to 9 kDa as recited in claim 20. The cited reference (whose authors include three of the present co-inventors) does not teach or suggest specific fractionation of copolymer-1, nor suggest any advantage to obtaining particular molecular weight fractions of copolymer-1 through the claimed method.

In response to the Examiner's comments concerning claim 20, the cited reference teaches a minimum molecular weight of 10 kilodaltons. In contrast, claim 20 requires a copolymer-1 having a molecular weight of about 5 to 9 kilodaltons. The cited reference does not teach or suggest obtaining the claimed molecular weight fraction of claim 20, nor provide a

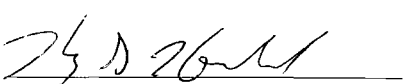
means to obtain a particular desired molecular weight fraction, as recited in claim 17. Accordingly, Applicants respectfully request that the Examiner withdraw this obviousness rejection.

The presently claimed invention is neither taught nor suggested by the cited art, and fully meets the requirements of 35 U.S.C. §112. Accordingly, Applicants request withdrawal of the outstanding rejections and allowance of this application.

Any questions or comments concerning this submission should be directed to the undersigned at the telephone number listed below.

Respectfully submitted,

Dated: July 14, 1997

By: 
Henry S. Hadad (Reg. No. 35,888)

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122709-1

EXHIBIT 2

PATENT
1662/46605

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#6/C
8/10/99
Frmeuan

Applicants	:	Eliezer KONFINO et al.
Serial No.	:	09/032,334
Filed	:	February 27, 1998
For	:	COPOLYMER 1: IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS
Examiner	:	F. Krass
Art Unit	:	1614

Assistant Commissioner for Patents
Washington D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on
Date: 2 August 1999 Reg. No. 38,607
Signature: [signature]
Pamela G. Salkeld

AMENDMENT UNDER 37 C.F.R. 1.111

Sir:

This amendment is responsive to the Office Action dated February 2, 1999 in the above-captioned application. A request for a three-month extension of time is being filed concurrently herewith. Please amend the application as follows:

IN THE CLAIMS:

replaced by DZ

17. (Amended) A method of manufacturing copolymer-1 of a predetermined [desired] molecular weight profile, comprising the steps of:

selecting a predetermined molecular weight profile;

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl

copolymer-1 having the predetermined [desired] molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction,

treating said trifluoroacetyl copolymer-1 having the predetermined [desired] molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined [desired] molecular weight profile.

20. (Amended) A method of manufacturing trifluoroacetyl copolymer-1 having a predetermined [desired] molecular weight profile, comprising the step [steps] of reacting protected copolymer-1 with hydrobromic acid for a time and at a temperature predetermined by test reaction.

21. (Amended) The method of claim 21, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26°C.

[purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.]

REMARKS

The Examiner is thanked for his consideration of the Information Disclosure Statement submitted in the present application on August 18, 1998. However, it is noted that the Examiner did not initial the last two references cited on the 1449 form. In order to ensure that all of the references listed in the Information Disclosure Statement are made of record in the present application, Applicants hereby resubmit the PTO Form 1449 attached to the Office Action dated

February 2, 1999. Applicants direct the Examiner to the fourth page of the 1449 form, and request that the Examiner indicate consideration of all references listed thereon.

Claims 17-22 are all of the claims pending in this application. The presently claimed invention is directed to a method of manufacturing copolymer-1 having a desired molecular weight profile. The presently claimed invention is also directed to a method of manufacturing trifluoroacetyl copolymer-1 having a desired molecular weight profile.

I. ENABLEMENT REJECTION

Claims 17-22 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner alleges that while claims 17 and 20 require that time and temperature be predetermined by a "test" reaction, the specification "lacks an adequate written description of specific procedures such that one could practice the invention." (2/2/99 Office Action at page 2).

Applicants respectfully traverse this rejection on the basis that one of ordinary skill in the art would recognize that the test reaction is a small-scale version of the method taught in the specification, performed in order to determine the appropriate time and temperature to obtain copolymer-1 having the desired profile. The Examiner has not provided any basis as to why one of ordinary skill in the art would be unable to follow this procedure taught by the present application in order to make copolymer-1 or trifluoroacetyl copolymer-1 of a desired molecular weight. As noted by the Examiner, pages 8-9 of the specification teach the use of test reactions over a time period and temperature in order to assess the exact parameters which provide copolymer-1 of a particular molecular weight profile; *e.g.*, 17 hours at 26°C to provide

copolymer-1 having a molecular weight fraction of 5 to 9 kDa. This assessment allows individuals of ordinary skill in the art to perform larger scale reactions and obtain large volumes of copolymer-1 of a desired molecular weight. Since one of ordinary skill in the art would know how to make and use the claimed invention without undue experimentation in view of the specification and the knowledge in the art, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph rejection.

II. INDEFINITENESS REJECTION

Claims 17-22 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. The Examiner has pointed to four specific claim terms, as well as a punctuation error, as the basis for this rejection. Each of these are addressed below.

First, the Examiner objects to the term "desired" as a relative term, alleging that the "term is not defined by the claims, the specification does not provide a reasonable standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner recommends that the term --predetermined-- be used instead."

The Examiner is thanked for this suggestion, which has been adopted. It is believed that the substitution of "predetermined" for -- desired -- clarifies that the molecular weight profile of the product of the claimed method one that is predetermined by a test reaction, as discussed above.

The Examiner also objects to the term "molecular weight profile," alleging that

"there are many possible determinations including polydispersity, absolute weight ranges, distribution by light scattering, etc., and the specification provides no guidance as to when a given 'profile' will be within the scope of the claims and when it will not." (2/2/99 Office Action at pages 2-3). Applicants respectfully traverse this rejection on the basis that one of ordinary skill in the art would understand the scope of the term "molecular weight profile," in view of the disclosure in the specification and knowledge in the art.

The term "molecular weight profile" is readily understandable to one of ordinary skill in the art; *i.e.*, that the presently claimed product is made by a process that allows one to choose and obtain a particular molecular weight profile of copolymer-1 or trifluoroacetyl copolymer-1. The molecular weight profile represents the percentage of copolymer-1 or trifluoroacetyl copolymer-1 having a molecular weight above a given amount. It may be determined using any method known to those in the art.

The Examiner has not offered any basis as to why one of ordinary skill in the art would not understand the scope of the term "molecular weight profile." In contrast, the specification provides guidelines as to how to obtain product of a desired molecular weight profile. Since one of ordinary skill in the art would understand the metes and bounds of the term "molecular weight profile," Applicants submit that this term is definite as required by 35 U.S.C. §112, second paragraph.

Third, the Examiner alleges that claims 17 and 20 are "incomplete insofar as they do not include any positive process steps associated with the recited 'test' reactions." (2/2/99 Office Action at page 3). It is believed that no such recitation is necessary, because one of ordinary skill in the art would be able to perform the recited test reaction, as discussed in the

"Enablement Rejection" section, *supra*.

Fourth, the Examiner states that in claim 20, second line, "'steps' is confusing insofar as only one singular step is actually recited." The claim has been amended to replace "steps" with –step–.

Fifth, the Examiner states that claim 22 is confusing since the second line ends in a period. Claim 22 was intended to end at the period at the end of the second line. The two lines following the period were placed there in error during the preparation of the application, and the claim has been amended to delete them.

III. ANTICIPATION REJECTION

On page 3 of the Office Action, the Examiner rejects claims 17-20 as being anticipated by U.S. Patent No. 3,849,550 to Teitelbaum *et al.* (the "'550 patent"). Applicants respectfully traverse this rejection, and submit that the presently claimed method is neither taught nor suggested by the cited reference for at least the following reasons.

As described above, the presently claimed method is directed to pre-determining by small scale reaction the time and temperature of the reaction of protected copolymer-1 with hydrobromic acid to form trifluoracetyl copolymer-1. This reaction allows for the production of copolymer-1 of the desired molecular weight fraction. In contrast to a mere purification, the presently claimed method allows for the precise fractionation of copolymer-1 to produce a particular molecular weight range of copolymer-1. The cited reference (whose authors include three of the present co-inventors) does not teach or suggest specific fractionation of copolymer-1, nor suggest any advantage to obtaining particular molecular weight fractions of copolymer-1 through the claimed method.

The cited reference teaches a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention relates to a copolymer-1 having over 75% of its molar fraction within the molecular weigh range of about 2kDa to about 20kDa and having an average molecular weight of about 4 kDa to about 8.6 kDa. The cited reference does not teach or suggest obtaining the molecular weight fraction of the presently-claimed invention nor provide a means to obtain a particular desired molecular weight fraction. Accordingly, Applicants respectfully request that the Examiner withdraw this anticipation rejection.

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 17-22 have been rejected under the judicially-created doctrine of obviousness-type double patenting. This rejection is traversed since the claims as amended in an independent and distinct from the claims of the '550 patent and the double-patenting rejection is therefore improper.

The test for obviousness-type double-patenting is whether any claim in the application defines merely an obvious variation of the invention disclosed and claimed in the issued patent, *i.e.*, whether that thing has been modified in any obvious manner. If the answer is no, there is no double patenting and no terminal disclaimer need be filed. *In re Vogel*, 164 USPQ 619, 622 (CCPA 1970); *In re White*, 160 USPQ 417, 418 (CCPA 1969). Since the compounds claimed in the present application and the '550 patent are distinctly different and the pharmacological properties of the present compounds are not obvious in view of the compounds disclosed and described in the '550 patent, claims 17-22 do not present a double-patenting situation. Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

The presently claimed invention is neither taught nor suggested by the prior art, and fully meets the requirements of 35 U.S.C. § 112. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections and allowance of this application.

Any inquiry concerning this submission should be directed to the undersigned at the telephone number listed below.

Respectfully submitted,

KENYON & KENYON

Date: 2 August 1999 By: Pamela G. Salkeld

Pamela G. Salkeld
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81664-1

EXHIBIT 3

Docket No.: 1662/46607

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors	:	Konfino, et al.
Serial No.	:	09/510,141
Filing Date	:	February 22, 2000
For	:	Copolymer-1: Improvements In Compositions of Copolymers
Examiner	:	Krass
Art Unit	:	1614

Assistant Commissioner
for Patents
Washington D.C. 20231

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December 18, 2000

Steven J. Lee (31,272)

AMENDMENT UNDER 37 C.F.R. § 1.111

SIR:

This Amendment is in response to the Office Action dated June 19, 2000, in the above-identified application. A petition for a three month extension of time, including the required fee, is being filed concurrently herewith. The extended date for response to the Action therefore expires on December 19, 2000.

Please amend the above-identified application as indicated below.

In the Claims:

Please cancel claim 19

Please amend claim 17; and add new claim 21 as follows:

B1

17. (Amended) A method for treating multiple sclerosis, comprising administering to a subject in need thereof, a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons[.]; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons.

B2

21. (New) The method according to claim 17, wherein said copolymer-1 fraction is prepared by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and

treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

REMARKS

Reconsideration of the subject patent application in light of the present Amendment and Remarks, which have been made to place this application in condition for allowance, is respectfully requested. Claim 17 has been amended to incorporate the limitations of dependant claim 19 to more particularly describe the present invention. New claim 21 has been added by amendment herewith. Support for this claim may be found throughout the specification.

Referring now to the Office Action, claims 17-19 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 3,849,550 to Teitlebaum *et al.* ("the '550 patent"). Applicants respectfully traverse this rejection and submit that the presently claimed method is

neither taught nor suggested by the '550 patent for at least the following reasons.

The presently claimed invention is directed to a method for treating multiple sclerosis, comprising administering to a subject in need thereof, a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons. The cited reference (whose authors include three of the present co-inventors) does not teach or suggest a method for treating multiple sclerosis comprising the specific copolymer-1 fractions presently claimed, nor suggest any advantage to a method for treating multiple sclerosis comprising the specific copolymer-1 fractions presently claimed.

The '550 patent teaches a copolymer-1 with a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention of independent claim 1 relates to a method wherein the copolymer-1 fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons. Additionally, the presently claimed invention of dependent claim 21 further relates to the method of 17 wherein said copolymer-1 fraction is prepared by a process comprising the steps of: (i) reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction; and (ii) treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa. The '550 patent does not teach or suggest obtaining the molecular weight fraction of the presently-claimed invention nor provide a method of treating multiple sclerosis comprising administering molecular weight fraction of the presently-claimed invention. Accordingly, applicants submit that pending claim 17, 18, 20 and 21 are not anticipated by the '550 patent and respectfully request that the Examiner withdraw this

anticipation rejection.

Claims 17-20 were rejected under 35 U.S.C. 102(b) as being anticipated by European Patent Application 0 383 620 (the '620 application). Applicants respectfully traverse this rejection and submit that the presently claimed method is neither taught nor suggested by the '620 application for at least the following reasons.

The '620 application relates to the preparation of recombinant copolymer-1 using ligated nucleotides. The copolymer-1 so produced is distinguished from copolymer-1of pending claims 17, 18, 20 and 21 insofar as the statistical linear distribution within the copolymer-1 structure will differ. The copolymer-1 of the '620 application does not have a random amino acid composition, but rather is derived from blocks of nucleotides, for example blocks of 9 nucleotide duplexes, 9-mers (the '620 application; page 5, line 21) which results in copolymer-1 having an arrangement of specific blocks of polypeptide sequences, for example KKA, EAE, KAK and YKK (page 8, lines 21-23). Therefore, since the copolymer-1 of the present application is not composed specific blocks of polypeptides sequences, it is clearly distinguished over the copolymer-1 disclosed in the '620 patent. In addition, the '620 application exemplifies the preparation of copolymers having molecular weights of 23,00 (page 5, lines 28-34). Applicants have demonstrated unexpectedly superior results for copolymers having lower molecular weights as shown in the examples set forth in the present application. Accordingly, applicants submit that pending claims 17, 18, 20 and 21 are not anticipated by the '620 application and respectfully request that the Examiner withdraw this anticipation rejection.

In view of the foregoing, Applicants submit that all of the pending claims of the subject application are now in condition for allowance, and issuance of a Notice of Allowance is respectfully requested. The Examiner is invited to telephone the undersigned attorney at (212) 908-6305 if there are any questions concerning this amendment.

Respectfully submitted,

Date: 12/18/00

Steven J. Lee
Reg. No. 31,272

KENYON & KENYON
One Broadway
New York, NY 10004
(212) 425-7200

EXHIBIT 4

6/B C/M 12-18-00

Patent
Docket No.: 1662/466071

Dat 1-9-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors	:	Konfino, et al.
Serial No.	:	09/510,466
Filing Date	:	02/22/00
For	:	COPOLYMER -1: IMPROVEMENTS IN COMPOSITION OF COPOLYMER
Examiner	:	F. Krass
Art Unit	:	1614

Assistant Commissioner
for Patents
Washington D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

December 18, 2000. SJL

Steven J. Lee (Reg. No.31,272)

AMENDMENT UNDER 37 C.F.R. § 1.111

SIR:

This Amendment is in response to the Office Action dated June 20, 2000, in the above-identified application. A petition for a three month extension of time, including the required fee, is being filed concurrently herewith. The extended date for response to the Action therefore expires on December 20, 2000.

Please amend the above-identified application as indicated below.

In the Claims:

Please cancel claim 19.

Please amend claim 17, and add new claim 21 as follows:

B1

17. (Amended) A composition for the treatment of multiple sclerosis comprising a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons[.]; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons.

B2

21. (New) The composition according to claim 17, wherein said copolymer-1 fraction is prepared by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and

treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

REMARKS

Reconsideration of the subject patent application in light of the present Amendment and Remarks, which have been made to place this application in condition for allowance, is respectfully requested.

Claim 17 has been amended to incorporate the limitations of dependent claim 19 to more particularly describe the present invention. New claim 21 has been added by amendment herewith. Support for this claim may be found throughout the specification.

Referring now to the Office Action, claims 17-19 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 3,849,550 to Teitlebaum et al ("the '550 patent"). Applicants respectfully traverse this rejection, and submit that the presently claimed method is

neither taught nor suggested by the cited reference for at least the following reasons.

The presently claimed invention is directed to a composition for the treatment of multiple sclerosis comprising a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons. The '550 patent (whose authors include three of the present co-inventors) does not teach or suggest a method for treating multiple sclerosis comprising the specific copolymer-1 fractions presently claimed, nor suggest any advantage to a composition for the treatment of multiple sclerosis comprising the specific copolymer-1 fractions presently claimed.

The '550 patent teaches copolymer-1 with a minimum molecular weight of 10 kilodaltons. In contrast, the presently-claimed invention of independent claim 17 relates to a composition for the treatment of multiple wherein the copolymer-1 fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons. Additionally, the presently-claimed invention of dependent claim 21 further relates to the compositions of claim 17 wherein said copolymer-1 fraction is prepared by a process comprising the steps of: (i) reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and (ii) treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa. The '550 patent does not teach or suggest obtaining the copolymer-1 molecular weight fraction of the presently-claimed invention nor provide a method of treating multiple sclerosis comprising administering molecular weight fraction of the presently-claimed invention. Accordingly, applicants submit that pending claims 17, 18, 20 and 21 are not anticipated by the

'550 patent and respectfully request that the Examiner withdraw this anticipation rejection.

Claims 17-20 were rejected under 35 U.S.C. 103(a) as being obvious in view of European Patent Application 0 383 620 (the '620 application). Applicants respectfully traverse this rejection and submit that, the presently claimed method of is neither taught nor suggested by the '620 application for at least the following reasons.

The '620 application relates to the preparation of recombinant copolymer-1 using ligated nucleotides. The copolymer-1 so produced is distinguished from the copolymer-1 of pending claims 17, 18, 20 and 21 insofar as the statistical linear distribution within the copolymer-1 structure will differ. The copolymer-1 of the '620 patent does not have a random amino acid composition, but rather is derived from blocks of nucleotides, for example blocks of 9 nucleotide duplexes, 9-mers (page 5, line 21) which results in copolymer-1 having an arrangement of specific blocks of polypeptide sequences, for example KKA, EAE, KAK and YKK (page 8, lines 21-23). Therefore, since the copolymer-1 of the present application is not composed of specific blocks of polypeptides sequences, it is clearly distinguished over the copolymer-1 disclosed in the '620 patent. In addition, the '620 application exemplifies the preparation of copolymers having molecular weights of 23,00 (see page 5, lines 28-34). Applicants have demonstrated unexpectedly superior results for copolymers having lower molecular weights as shown in the examples set forth in the present application. Accordingly, applicants submit that pending claims 17, 18, 20 and 21 are not obvious in view of the '620 application and respectfully request that the Examiner withdraw this anticipation rejection.

Claims 17-20 have been rejected under the judicially-created doctrine of obviousness-type double patenting. This rejection is traversed since the claims as amended are independent and distinct from the claims of U.S. Patent Nos. 5,981,589, and 6,054,430 and the double-patenting rejection is therefore improper.

The test for obviousness-type double-patenting is whether any claim in the application defines merely an obvious variation of the invention disclosed and claimed in the issued patent, *i.e.*, whether that thing has been modified in any obvious manner. If the answer is no, there is no double patenting and no terminal disclaimer need be filed. *In re Vogel*, 164 USPQ 619, 622

(CCPA 1970); *In re White*, 160 USPQ 417, 418 (CCPA 1969). Since the compounds claimed in the present application and the 5,981,589, and 6,054,430 patents are distinctly different the present compounds are not obvious in view of the compounds disclosed and described in U.S. Patent Nos. 5,981,589, and 6,054,430, pending claims 17, 18, 20 and 21 do not present a double-patenting situation. Accordingly, withdrawal of this rejection is respectfully requested.

In view of the foregoing, applicants submit that all of the pending claims of the subject application are now in condition for allowance, and issuance of a Notice of Allowance is respectfully requested. The Examiner is invited to telephone the undersigned attorney at (212) 908-6305 if there are any questions concerning this amendment.

Respectfully submitted,

Date: 12/18/00

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304851

EXHIBIT 5

This exhibit is filed under seal
pursuant to the April 10, 2009 Protective Order

EXHIBIT 6

Third, cytotoxic lymphocytes, but no PFC, appear when thymus cells are transferred in irradiated allogenic recipients [6]. Fourth, treatment of immune spleen cells with anti-Θ serum and complement, which results in selective destruction of thymus-derived cells active in CMI [15], abolishes *in vitro* cytotoxicity without affecting the 19 S allo-antibody-forming cells (PFC).

Received March 19, 1971.

5. References

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15 Cerottini, J.-C., Nordin, A. A. and Brunner, K. T. *Nature* 1970. *228*: 1308.

Dvora Teitelbaum, A. Meshorer, T. Hirshfeld+, Ruth Arnon and M. Sela

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot

Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide*

Three random basic copolymers of amino acids were tested for their effect on experimental allergic encephalomyelitis (EAE). One of these copolymers denoted as Cop 1, composed of alanine, glutamic acid, lysine and tyrosine, with a molecular weight of 23 000, showed a marked suppressive effect on the disease. The intravenous administration of Cop 1 in physiological saline, as late as 5 days following the challenge with the disease-inducing dose of the basic encephalitogenic protein, reduced the clinical incidence of EAE from 64 % in the control group to 22 %; the histological lesions were also decreased both in prevalence and in severity. The suppressive effect on the disease attained by the synthetic copolymer is of the same order of magnitude as that previously reported for the basic encephalitogen.

The effect of the copolymers appears to be specific, since neither an acidic amino acid copolymer, nor unrelated basic proteins, had any protective action. On the other hand, a second batch of Cop 1 showed activity identical to that of the first batch. The potential applicability of this non-encephalitogenic and non-immunosuppressive material is discussed.

1. Introduction

Experimental allergic encephalomyelitis (EAE) is an acute neurological autoimmune disease induced in laboratory animals by a single injection of brain or spinal cord tissue in complete Freund's adjuvant [1, 2]. The disease is characterized clinically by paralysis of the hind legs and histologically by perivascular infiltration in the brain tissue [2].

* Supported in part by the Freudenberg Foundation.
+ Recipient of a long-term EMBO fellowship.

Correspondence: Ruth Arnon, Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot, Israel

Abbreviations: EAE: Experimental allergic encephalomyelitis **BE:** Basic encephalitogen **Cop 1:** Copolymer 1 **Cop 2:** Copolymer 2 **Cop 3:** Copolymer 3 **AGT:** An acidic copolymer of alanine, glutamic acid and tyrosine **LDH:** Lactic dehydrogenase **ICFA:** Incomplete Freund's adjuvant **CFA:** Complete Freund's adjuvant.

The active encephalitogenic component in the nervous tissue is a basic low molecular weight protein which is a constituent of myelin, and has been purified by various procedures [3–7]. The basic encephalitogen (BE) is active in extremely low doses. Thus, 1–10 μg injected per guinea pig will induce the clinical symptoms, and a dose as low as 0.1 μg per guinea pig will bring about histological changes [6]. In recent years a number of reports appeared, demonstrating that high doses of the same protein injected by a different route can either suppress or prevent the induction of EAE [8–10]. Recently it was found that not only the basic encephalitogen was effective in such treatment, but other non-encephalitogenic basic neural proteins had a similar protective effect when injected in incomplete Freund's adjuvant [10]. In contrast, basic proteins of non-neural origin, such as histones, did not provide any protection.

In view of these results we have synthesized three random copolymers, of amino acid compositions approaching, to a

certain extent, that of the natural encephalitogen, and possessing a positive net electrical charge. The copolymers were tested for possible encephalitogenic activity, as well as for their capacity to suppress the disease. None of the copolymers had any encephalitogenic activity. On the other hand, these synthetic models were effective in suppressing EAE. The present report describes the effectiveness and specificity of this protective action.

2. Materials

2.1. Animals

D. H. Albino guinea pigs weighing 300–400 g were used in all the experiments, unless otherwise stated.

2.2. Proteins

The basic encephalitogenic protein (BE) was prepared from bovine spinal cord, as described previously [7], by column chromatography on SE-Sephadex (Pharmacia, Uppsala). The amino acid composition of this protein [7] is: $Lys_{12}His_8Arg_{16}Asp_{10}Thr_6Ser_{14}Glu_{10}Pro_{11}Gly_{21}Ala_{12}Val_2Met_2Leu_3Leu_9Tyr_3Phe_7Trp_1$, with a calculated molecular weight of approximately 16 000. Hen egg-white lysozyme (2 x crystallized) was obtained from Worthington Biochemicals, N. J. Bovine pancreatic ribonuclease (RNase type I–A, 5 x crystallized), and cytochrome *c* (from horse heart, type II) were from Sigma Chemical Co.

2.3. Copolymers

Four different random copolymers of amino acids were used in this study. Three were rich in basic amino acids, whereas the fourth one was an acidic copolymer. They were prepared from the N-carboxyanhydrides of the respective amino acids according to Katchalski and Sela [11].

2.3.1. Copolymer 1

Cop 1 was prepared from the N-carboxyanhydrides of tyrosine [12], alanine [13], γ-benzyl glutamate [14], and ε, N-trifluoroacetyllysine [15] (Table 1). The polymerization reaction was carried out at room temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl groups of the glutamic acid was carried out with hydrogen bromide in glacial acetic acid [16], and was followed by the removal of the trifluoroacetyl groups from the lysine residues by 1 M piperidine [17]. A second batch of this polymer was prepared in an identical manner. The molecular weight and amino acid composition of these polymers are listed in Table 1.

2.3.2. Copolymer 2

Cop 2 was prepared from the N-carboxyanhydrides of the following amino acids (Table 2): ε, N-trifluoroacetyllysine, N-benzylhistidine [18], O-benzylserine [19], γ-benzyl glutamate, proline [12], glycine [20] and tyrosine, by polymerization in dioxane (dimethylamine as initiator). In the first deblocking stage the benzyl groups were removed by hydrogen bromide in glacial acetic acid [16] to liberate the carboxy groups of glutamic acid and the hydroxyl groups of serine. In the second stage the benzyl groups were removed from the histidine residues by hydrogenation with palladium as catalyst. The trifluoroacetyl groups were removed from the lysine residues by 1 M piperidine.

Table 1. Composition of copolymer 1

Amino acid	N-Carboxyanhydride derivative used for reaction	Amount used in the reaction		Molar ratio of amino acid in co-polymer	
		g	mM	Batch I	Batch II
Alanine	Alanine	8.6	75	6.0	6.7
Glutamic acid	γ-Benzyl glutamate	6	23	1.9	2.1
Lysine	ε,N-Trifluoroacetyl-lysine	14	52	4.7	4.2
Tyrosine	Tyrosine	3	14	1.0	1.0
Molecular weight				23100	22800

Table 2. Composition of copolymer 2

Amino acid	N-Carboxyanhydride derivative used for reaction	Amount used in the reaction		Molar ratio of amino acid in co-polymer
		g	mM	
Glutamic acid	γ-Benzyl glutamate	7.9	30	2.0
Glycine	Glycine	4.5	22	1.4
Histidine	N-Benzylhistidine	6.7	22	0.4
Lysine	ε,N-Trifluoroacetyl-lysine	10.1	37	2.8
Proline	Proline	2.1	15	0.4
Serine	O-Benzylserine	4.9	22	1.1
Tyrosine	Tyrosine	3.0	14	1.0
Molecular weight				4000

Table 3. Composition of copolymer 3

Amino acid	N-Carboxyanhydride derivative used for reaction	Amount used in the reaction		Molar ratio of amino acid in co-polymer
		g	mM	
Alanine	Alanine	3.5	30	4.0
Arginine	δ, N-Trifluoroacetyl ornithine	7.5	29	1.0
Aspartic acid	β-Benzyl aspartate	5	20	2.7
Glutamic acid	γ-Benzyl glutamate	5.2	20	3.2
Glycine	Glycine	6	59	6.5
Histidine	N-Benzylhistidine	9.2	30	1.7
Leucine	Leucine	1.6	10	1.0
Lysine	ε-Carbobenzyloxy-lysine	6	20	3.8
Phenylalanine	Phenylalanine	1.9	9	1.2
Proline	Proline	2.8	20	1.8
Serine	O-Benzylserine	6.6	30	3.9
Tyrosine	Tyrosine	2.8	14	1.0
Molecular weight				5000

2.3.3. Copolymer 3

Cop 3 was prepared by the random polymerization in dioxane of the N-carboxyanhydrides of the following amino acids: alanine, N-trifluoroacetylornithine [21], β-benzyl aspartate [22], γ-benzyl glutamate, glycine, N-benzylhistidine, leucine [23], ε-carbobenzoxylysine [11], phenylalanine [11], proline, O-benzylserine and tyrosine (Table 3). The first deblocking stage was treatment with 1 M piperidine for the removal of the trifluoroacetyl groups from the δ-amino groups of the ornithine residues. They were subsequently guanidinated with 1-guanyl-3,5-dimethylpyrazol nitrate [21] to form arginine residues. The second deblocking stage was treatment with hydrogen bromide in glacial acetic acid. This liberated the carboxyl groups of glutamic and aspartic acids, the hydroxyl groups of serine and the amino groups of lysine. The benzyl groups of the histidine were then removed by hydrogenation.

The amino acid composition and molecular weights of copolymers 2 and 3 are listed in Tables 2 and 3, respectively.

The acidic copolymer, poly($Ala^{33}Glu^{37}Tyr^{30}$) [24], abbreviated as AGT, was a gift from Dr. Sara Fuchs. It had an average molecular weight of 17 000.

3. Methods

3.1. Induction of EAE

Guinea pigs were injected with 10 μg of the purified BE in complete Freund's adjuvant into the footpads of the two hind legs. They were then observed daily for loss in weight, and for the appearance of clinical symptoms of the disease, as reflected by paralysis of the hind legs.

3.2. Delayed hypersensitivity reactions [25]

The skin test reactions were carried out on the 10th or the 11th day after the challenge injection. The basic encephalitogen (20 μg in 0.1 ml saline) was injected intradermally into each of the guinea pigs. The appearance of erythema at the spot of the injection was observed 24 h later, and the extent of the delayed hypersensitivity was quantitated by measuring the diameter of the skin reaction. Only reactions of above 5 mm diameter were considered positive.

3.3. Determination of lactic dehydrogenase (LDH) activity

The level of LDH in the sera of the guinea pigs was assayed spectrophotometrically by the rate of oxidation of the reduced form of nicotinamide adenine dinucleotide (NADH) after adding sodium pyruvate to the serum, according to Schwartz and Bodansky [26]. The determinations were carried out on sera from bleedings at days 4, 11 and 14 after the induction of EAE. A rise in value of LDH was observed only in samples from the 14th day.

3.4. Histological tests

The animals were sacrificed after 4 weeks by means of nembutal. The brain was taken out in its entirety after the skull had been sawn. The *medulla oblongata* was also removed till the atlas. After fixation of the brain in formalin for a period of 24 h a median section was taken 3 mm from the center line (along the *sulcus lateralis*). A whole median section of this area was put into formalin for an additional period of 24 h. Cross-sections were also taken for fixation from the following areas: a cross-section along the line of the *vermis*, the *corpus mamillare*, the *tuberculum olfactorium* and of the *medulla oblongata*. The sections were stained with Luxol-fast-blue [27] with counter stain "kern echt rot".

All histological examinations were carried out under code. The histopathological changes which we observed were: in mild cases (+) a small percentage of blood vessels showed a slight perivascular infiltration with mononuclear cells (Consisting mainly of small lymphocytes and very few granulocytes (Fig. 1 b). The perivasculitis could be observed in different parts of the brain without any predominating area. Figure 1 a shows, for comparison, a normal blood vessel in the control brain tissue.

In more advanced cases (++) the histological changes were much more obvious in comparison to the former group, namely, a higher percentage of the blood vessels were affected and the infiltrated area around them was thicker.

In severe cases (+++) the perivasculitis was very massive (Fig. 1 c) together with periventriculitis (Fig. 1 d). The ventricles were surrounded by inflammatory cells, mainly with small lymphocytes and a few macrophages. In many places in the severe cases, groups of lymphocytes were seen in the brain parenchyma, not being a part of the immediate perivascular or periventricular zone (Fig. 1 e).

As mentioned, we used the Luxol-fast-blue dye to stain myelin, but no stage of demyelination appeared.

3.5. Prevention of EAE

Each animal received 8 repeated intradermal injections of 100 μg of the respective polymer in incomplete Freund's adjuvant (ICFA). The material was injected over the back and sternum of the guinea pigs twice a week for four weeks [10]. Three days after the last injection the animals were challenged with 10 μg of BE in CFA into the two hind footpads.

3.6. Suppression of EAE

After the initial challenge with 10 μg of BE, two methods of suppression were tried: (1) each guinea pig received 6 intradermal injections of 100 μg each of the respective polymer in incomplete Freund's adjuvant. The injections were given over the back and sternum of the guinea pig, twice a week for three weeks starting two days after the initial challenge [10]. (2) Each guinea pig received three intravenous injections of 1 mg each of the respective polymer or protein in saline. The injections were given according to schedules mentioned in the text, which differed in the various experiments.

3.7. Molecular weight determinants

The average molecular weights of the polymers were determined, in a Spinco model E ultracentrifuge, from sedimentation and diffusion measurements, as described earlier [24], and by the approach to equilibrium technique of Yphantis [29].

3.8. Amino acid analyses

Were carried out in a Beckman-Spinco automatic amino acid analyzer, Model 120-B, after hydrolysis of the samples under reduced pressure in constant boiling hydrochloric acid (6N) for 22 h [28].

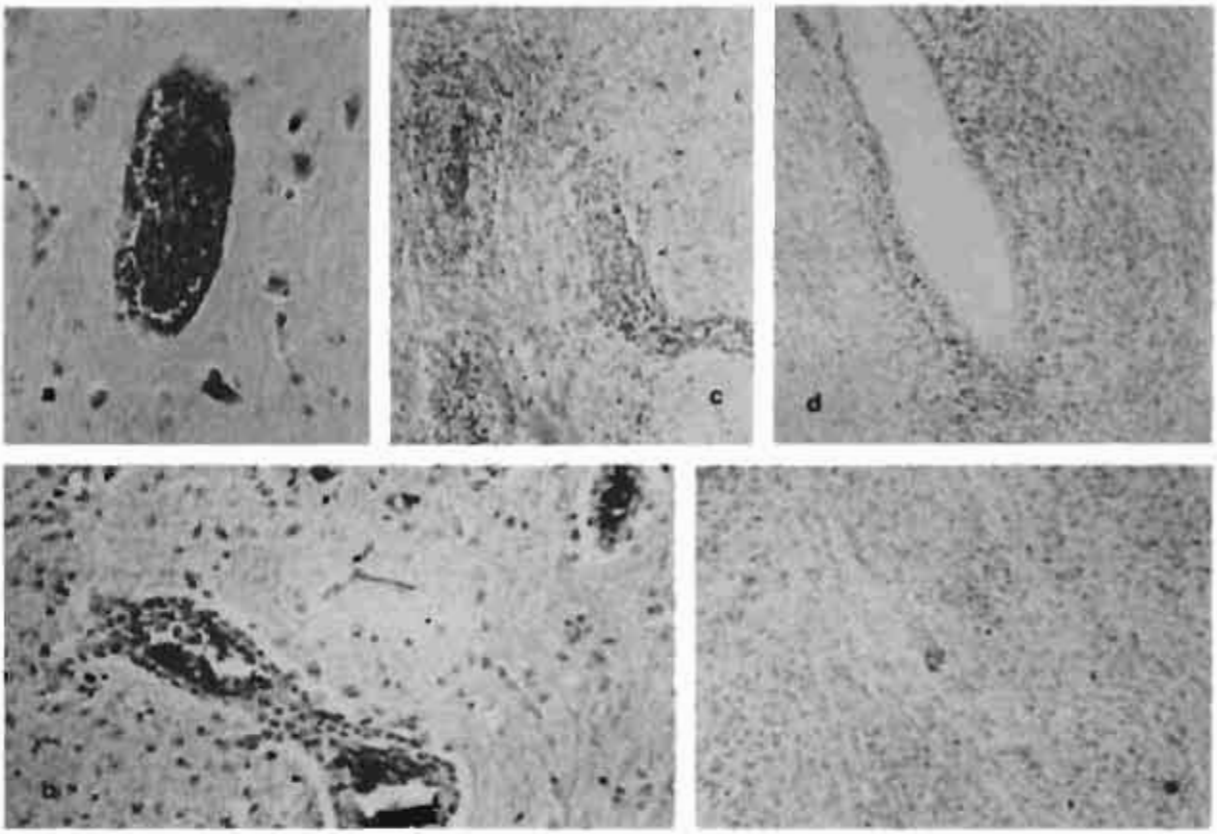

Figure 1. Typical examples of the histological changes in the brains of guinea pigs challenged with BE (the sections were stained with Luxol-fast-blue and counterstained with nuclear fast red).
a) A normal control; a normal blood vessel. (The erythrocytes are stained deep blue). Note the thin vessel wall containing the endothelial and epithelial layers only (magnification: x 500).
b) Perivasculitis; blood vessel from a mild positive case. Note the narrow mononuclear infiltration around the vessels (x 500).
c) Perivasculitis; a strong positive case. Note the thick inflammatory area (x 200).
d) Periventriculitis (x 200).
e) Diffuse mononuclear infiltration of the brain parenchyma (x 200).

4. Results

4.1. Characterization of EAE

In the numerous reports which have appeared in the literature on EAE, several criteria were used for the diagnosis of the disease. The appearance of clinical symptoms, manifested mainly by the paralysis of the hind legs, was the criterion mostly used. A second parameter reported is the degree of histological changes in the brain. It has also been suggested that in many cases a correlation exists between delayed hypersensitivity reaction toward the encephalitogen and the appearance of clinical symptoms [30]. Recently, it has been shown that the level of serum LDH in rabbits increased as a result of EAE [31], and could thus serve as a useful index of the disease induction.

We have determined all four parameters mentioned above in ten individual guinea pigs, and the results are presented in Table 4. As shown, six out of the ten animals were paralyzed within 13 to 20 days after being challenged with BE. Histological lesions, of various degrees of severeness, were observed in the brains of all the guinea pigs tested. Delayed hypersensitivity reaction was observed on 8 of the guinea pigs. However, it is of interest that the animals which gave negative results in the delayed hypersensitivity test suffered paralysis, whereas all four animals that did not show the clinical symptoms reacted positively in the delayed hypersensitivity test. An increase was observed in the level of serum lactic dehydrogenase in several of the animals. This effect could not be correlated, however, with the other parameters listed in Table 4.

On the basis of these and similar data, we have chosen the incidence of clinical symptoms and of histological lesions in the brain as the two critical parameters for evaluation of our results. All animals suffering from paralysis were considered diseased, and the non-paralyzed animals were judged by the degree of their histological lesions. An added indication of the disease was the decrease in the weight of the animals. This, however, was not considered to be of major significance, as it is not specific for EAE.

4.2. Encephalitogenic activity of the synthetic copolymers

The copolymers 1, 2 and 3 were tested for encephalitogenic activity at dose levels of 10 μg, 250 μg, 1 mg and 5 mg. Each dose of each copolymer was injected into 5 guinea pigs in CFA in the two hind legs. No clinical symptoms were observed and the histological results were all negative.

Table 4. Characterization of EAE

Guinea pig no.	Delayed hypersensitivity reaction[a]	Day of onset of paralysis	Histological lesions[b]	Lactate dehydrogenase[c] enzyme units	Weight change
1	negative	13	+	83	decrease
2	negative	14	+	124	decrease
3	6	20	+++	42	decrease
4	7	no paralysis	+	44	no decrease
5	8	no paralysis	++	80	decrease
6	8	17	++	86	decrease
7	12	15	+++	34	decrease
8	14	15	+++	136	decrease
9	15	no paralysis	+	33	no decrease
10	15	no paralysis	++	90	decrease

a) The test was carried out on the 11th day after challenge. The numbers represent the diameter of the skin reactions in mm.

b) The various degrees of the histological lesions are described and defined under methods.

c) The LDH was assayed in serum samples taken on the 14th day after challenge. The level of LDH in the sera of untreated guinea pigs was between 25 and 50 enzyme units.

Table 5. Prevention and suppression of EAE by synthetic copolymers

Group	Treatment	Copolymer	Clinical incidence	Histological changes
Control	Injection with 10 μg BE in CFA into the footpads of the animal	none	15/20	20/20
Prevention	Eight intradermal injections of 100 μg of the polymer in ICFA, twice a week for four weeks, followed by challenge with 10 μg of BE in CFA	Cop 1	3/9	8/9
		Cop 2	5/10	9/10
		Cop 3	5/10	9/10
Suppression	Injection with 10 μg BE in CFA, followed by 6 intradermal injections of 100 μg copolymer in ICFA, two injections per week, starting two days after the injection of BE	Cop 1	2/9	5/9
		Cop 2	4/10	10/10
		Cop 3	3/10	10/10
		ICFA alone	2/5	5/5

Table 6. Suppression of EAE by intravenous injections of polymers[a]

Treatment	Clinical incidence	Histological changes	
		Incidence	Degree
Control: 10 μg of BE	4/5	5/5	++, +++
Cop 1	1/5	4/5	+, ++
Cop 2	6/8	7/8	++, +++

a) The copolymers (1 mg) were injected intravenously at days 5, 10, 15 after challenge with BE.

4.3. Prevention and suppression of EAE with synthetic copolymers

In the first stage of this work experiments of prevention and suppression of EAE with the synthetic polymers were carried out under conditions identical with those described by Roboz-Einstein et al. [10]. The results are listed in Table 5. In the suppression experiment the copolymers were more effective. The best result was achieved with Cop. 1 which brought about reduction not only in the clinical incidence of the disease, but also in the prevalence of histological lesions.

The only doubt shed upon these data is the finding [32] that injection of incomplete Freund's adjuvant alone had a suppressive effect on EAE. Indeed, in the one experiment listed in Table 5, it was found to have a suppressive effect. For this reason an additional suppression experiment was carried out by applying intravenous injections of the copolymers in saline (Table 6). Only two copolymers (Cop 1 and Cop 2) were compared in this experiment, since Cop 3 was found toxic under the conditions employed. It is seen from Table 6 that under the experimental conditions used Cop 2 had no protecting effect against the disease. Cop 1, however, showed a drastic suppressive effect. It reduced the clinical incidence of the disease, as well as the degree of histological lesions.

4.4. Effect of schedule of injections

The effectiveness of Cop 1 was studied as a function of the schedule of the injections given for suppressing the EAE. The results given in Table 7 show that the injections of the suppressive agent may be started as late as 5 days after the challenge with the BE and still provide a protecting effect.

However, if the injections are started at 10 days after the challenge, the polymer is not effective any longer. The best conditions, as indicated by these experiments, are three injections of the material at days 5, 10 and 15 after the induction of EAE.

In later experiments it was found that when young guinea pigs (weighing less than 300 g) were used, the day of onset of paralysis occurred earlier (at days 12–15 as compared to days 15–21 in adult animals). In these cases the suppression injections have to be given at earlier dates, namely, days 1, 6 and 11 after the challenge.

4.5. Specificity of the suppressive effect

In an attempt to study the specificity of the suppressive effect, we first synthesized and tested another batch of Cop 1 prepared under the same conditions as the first one. The two batches of the polymer were shown to be similar in both amino acid composition and molecular weight (Table 1). In addition to the testing of the second preparation of Cop 1, we compared the efficiency of this suppression to that caused by the natural BE on the one hand, and by non-related materials on the other hand. The results listed in Table 8 show that the two batches of the polymer had similar activities. Both reduced considerably the clinical and histological symptoms of the disease to an extent comparable to the reduction effected by the natural

Table 7. Role of schedule of injections in EAE suppression

Treatment	Clinical incidence			Histological changes			
	Individual experiments	Total	%	Incidence	Total	%	Degree
Control: 10 μg of BE	3/5 4/5 3/5 4/7	14/22	64	5/5 5/5 5/5 7/7	22/22	100	++, +++
Cop 1 batch 1. Three injections of 1 mg given at days 1, 5, 10 after challenge with BE	1/5 2/5	3/10	30	3/5 4/5	7/10	70	+,++
Cop 1 batch 1. Three injections of 1 mg given at days 5, 10, 15 after challenge with BE	0/5 1/5 1/5 3/7	5/22	22	4/5 4/5 5/5 4/7	17/22	77	+, ++
Cop 1 batch 1. Two injections of 1 mg given at days 10, 15 after challenge with BE	3/5 3/5	6/10	60	4/5 5/5	9/10	90	++, +++

encephalitogen. In contradistinction, the synthetic acidic polymer AGT, of a similar molecular weight to Cop 1 but devoid of the basic lysine residues, did not provide any protective effect; of the three basic non-related proteins used in this study RNase was the only one that had a slight protective effect. It is not clear, however, what the *in vivo* effect of RNase is, due to its enzymative activity on nucleic acids. Neither lysozyme nor cytochrome *c* had any protective effect.

4.6. Additional remarks

A general phenomenon encountered in all the experiments described was the considerable loss of weight of animals with EAE, observed usually one day before paralysis occurred. In cases where protection against the disease was successful the loss of weight was less marked and lasted for only a few days, after which the animals regained weight.

Table 8. Specificity of EAE suppression

Treatment: Three injections of 1 mg at days 5, 10, 15 after challenge with BE	Clinical incidence		Histological changes		
	Total	%	Incidence	%	Degree
Control	14/22	64	22/22	100	++, +++
Cop 1 batch 1	5/22	22	17/22	77	+, ++
Cop 1 batch 2	3/13	23	11/13	85	+, ++
Basic encephalitogen (BE)	2/8	25	8/8	100	+, ++
Acidic copolymer AGT	10/13	77	13/13	100	++, +++
Lysozome	2/3	66	5/5	100	++, +++
RNase	7/13	54	12/13	92	++, +++
Cytochrome *c*	7/10	70	10/10	100	++, +++

Table 9. Effect of synthetic polymer on delayed hypersensitivity to BE

Treatment	Clinical incidence	Delayed hypersensitivity to BE	
		Incidence	Mean diameter (mm)
Control: 10 μg BE	24/36	32/36	11.2
Three injections of 1 mg of Cop 1, at days 5, 10, 15 after challenge with BE	11/40	34/40	10.4

The possible effect of Cop 1 on the development of delayed hypersensitivity towards the BE was also investigated. The results given in Table 9 show no such effect. Whereas the difference in the clinical incidence of EAE between the control and experimental group was very marked, the prevalence of delayed hypersensitivity was very similar in the animals suffering from EAE and in those where protection was effected.

5. Discussion

The data reported in this communication demonstrate that a preparation of a simple synthetic basic copolymer of amino acids has a marked suppressive effect of EAE when injected either intradermally or intravenously. Using the intradermal injections, administered in incomplete Freund's adjuvant, two other basic copolymers also had suppressing activity, which could not be demonstrated in experiments where the materials were injected intravenously in saline (Tables 5 and 6). However, the effect of the intradermal injections seems rather difficult to evaluate due to the suppressing effect incurred by the adjuvant alone under the same conditions (Table 5). For this reason, the results obtained by intravenous injections in saline are considered to be more reliable. Only one basic copolymer, Cop 1, has protective activity against EAE when injected intravenously, and this material does not bring about any apparent toxic effects in the treated animals.

The effect of this copolymer seems to be specific, as indicated by the fact that a second batch of the same material prepared under identical conditions and having the same amino acid composition and molecular weight, showed similar activity to that of the first one, while on the other hand, an acidic copolymer, AGT, with the same molecular weight but lacking in lysine, had no protective effect. As this may indicate that basicity is of importance, other basic proteins of similar molecular weight were also checked. The finding that none of these proteins had any protective effect (Table 8), and that only Cop 1 was effective under the conditions used in this study, indicate that the net

electrical charge of the molecule is not by itself sufficient in inducing the suppressive activity. It is possible, however, that the density of the charge on the surface of the molecule has a determining role.

EAE is generally associated with cellular immunity [2], and delayed hypersensitivity measurements serve as an important criterion in its determination [30]. From our results this correlation does not seem to be valid, as indicated in Table 4. Furthermore, the decrease of the incidence of EAE induced by Cop 1 is not associated with an equivalent suppression of delayed hypersensitivity to the basic encephalitogen (Table 9). These results seem to indicate that the suppression of EAE is not necessarily accompanied by a manifestation of delayed hypersensitivity, as suggested by Lisak et al. [33]. On the other hand, they are in agreement with the results of Chase [34], and of Caspary and Field [35], which raised doubts about the significance of the skin sensitivity test in EAE.

Copolymer 1 in itself is immunogenic and elicits, in rabbits, the production of specific antibodies. It has not yet been determined whether it is immunologically active in guinea pigs as well, and whether any cross-reaction exists between it and the natural encephalitogen. The problem is under investigation at present, and might serve as a clue in studies of the mechanism of the suppressive activity of the synthetic copolymer.

Animals protected by Cop 1 probably go through a state of a very mild manifestation of the disease, as indicated by a slight loss in weight and the mild histological lesions in the brain. The animals usually regain their weight within a few days, and after a period of about four weeks they return to a completely normal state. Preliminary data indicate that thereafter they remain protected against the disease, since a second challenge with a disease-inducing dose of the BE does not bring about any clinical effects. In that respect, the animals which were protected by the copolymer show the same behavior as animals which have recovered from a severe state of EAE and are subsequently resistant to the induction of a second attack [32, 36, 37].

The two general methods for suppressing EAE, which were previously described, are the use of immunosuppressive agents such as ALS [38], cyclophosphamide [39] or X-ray-irradiation [40] on the one hand, and the use of high doses of the encephalitogen itself, on the other hand [8, 10]. The use of a synthetic copolymer described here is advantageous over these two methods, since the polymer is devoid of encephalitogenic activity and is not immunosuppressive. Moreover, it is simple in composition and easy to synthesize. In its suppressive activity it is as effective as the BE itself, and thus may be of help both in studies of the mechanism of EAE and as a potential suppressive agent for EAE and other diseases of a similar nature.

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EXHIBIT 7

EXHIBIT 84

W-138

A 4966

IN THE UNITED STATES PATENT OFFICE

In re application of June 29, 1973

Dvora Teitelbaum et al Art Unit 125

Serial No. 240,244 Examiner: S. Friedman

Filed March 31, 1972

For: THERAPEUTIC COPOLYMER

Hon. Commissioner of Patents

Washington, D.C.

Sir:

Responsive to the Office Action of April 2, 1973, please amend the above-identified application as follows:

In the Abstract of the Disclosure:

Page 1, line 3, after "prevention of" insert - - certain - -

line 4, change "of" (first occurrence) to - - having - -

delete "of" (second occurrence)

change "15000, of" to - - 15000 and a - -

line 9, after "desired" insert a comma

In the Specification:

Page 1, delete lines 12 through 22; beginning with "FIELD OF THE INVENTION" and ending with "DESCRIPTION OF THE PRIOR ART"

Rewrite last three lines of page as follows:

Experimental allergic encephalomyelitis (EAE) is an autoimmune disease affecting the brain. EAE serves as a model disease for multiple sclerosis, post-infectious encephalitis, and subacute panencephalitis. Curative agents suitable for the treatment of EAE are of interest for the possible treatment of these further diseases.

EAE is induced in laboratory animals by an injection of brain tissue or by an -

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Page 2, rewrite line 13 to read - - treatment of allergic encephalomyelitis. - -

Delete the remainder of the page

Page 3, delete lines 1-11 (first two paragraphs)

line 12, rewrite to read - -

In accordance with the invention, there is provided a composition - -

line 13, delete "novel curative agent"

line 14, change "autoimmune...above," to - - EAE, - -

line 16, change "these severe" to - - the disease. - -

line 17, delete "diseases."

change "As set out above" to - - Alternatively, - -

delete "for"

line 18, rewrite to read - - to immunize against EAE. - -

line 20, change "autoimmune diseases of the" to - - EAE - -

line 21, delete "type defined above"

change "these" to - - this autoimmune disease - -

line 24, insert - - and - - after "18,000,"

line 26, change "an electrical negative" to - - a negative electrical - -

line 27, insert - - a - - after "as"

Page 4, lines 18 and 19, insert a period after "EAE" and delete "and EAE-type diseases."

Page 6, line 17, after "injected" insert - - with - -

line 18, change "was" to - - were periodically - -

change "1 day, after" to - - 1, - -

line 19, delete "each time a quantity of"

insert "quantities" after - - mg - -

line 23, rewrite to read - - against other autoimmune diseases of the same type. - -

last line, change "non-limitative" to - - non-limiting - -

In the Claims:

Rewrite the claims as follows:

11. A water-soluble copolymer useful in the treatment or prevention of experimental allergic encephalomyelitis, said polymer having a molecular weight in excess of 15,000, a net positive electrical charge, and being selected from the group consisting of polymerizates of mixtures consisting essentially of (1) alanine, glutamic acid, lysine and tyrosine; (2) alanine, aspartic acid, lysine and tyrosine; and (3) alanine, glutamic acid and lysine.

12. The polymer of Claim 11, consisting essentially of a polymer of mixture (1) thereof, in the molar ratio of about 6 parts alanine to two parts glutamic acid to 4.5 parts lysine to 1 part tyrosine.

13. The polymer of Claim 11, consisting essentially of a polymer of mixture (2) thereof, in the molar ratio of about 5 parts alanine to 1.5 parts aspartic acid to 3.5 parts lysine to 1 part tyrosine.

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14. The polymer of Claim 11 consisting essentially of a polymer of mixture (3) thereof, in the molar ratio of about 5 parts alanine to 1.5 parts glutamic acid to 3.5 parts lysine.

15. A therapeutic preparation for use in the treatment or prevention of experimental allergic encephalomyelitis, comprising a water-soluble copolymer having a molecular weight in excess of 15,000, a net positive electrical charge, and being selected from the group consisting of polymerizates of mixtures consisting essentially of (1) alanine, glutamic acid, lysine and tyrosine; (2) alanine, aspartic acid, lysine and tyrosine; and (3) alanine, glutamic acid and lysine; in an amount effective for treatment or prevention of the said disease, dispersed in a pharmaceutically acceptable carrier for injectable administration.

~~16.~~ A therapeutic preparation for use in the treatment or prevention of experimental allergic encephalomyelitis, comprising the composition set forth in Claim 15, wherein the copolymer, ~~consists essentially of a polymer~~ is the copolymer of alanine, glutamic acid, lysine and tyrosine ~~in the molar ratio of about 6 parts alanine to 2 parts glutamic acid to 4.5 parts lysine to 1 part tyrosine~~.

~~17.~~ A therapeutic preparation for use in the treatment or prevention of experimental allergic encephalomyelitis, comprising the composition set forth in Claim 15, wherein the copolymer ~~consists essentially of a polymer~~ is the copolymer of alanine, aspartic acid, lysine and tyrosine ~~in the molar ratio of about 5 parts alanine to 1.5 parts aspartic acid to 3.5 parts lysine to 1 part tyrosine~~.

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~~18~~. A therapeutic preparation for use in the treatment or prevention of experimental allergic encephalomyelitis, comprising the composition set forth in Claim ~~17~~ 1, wherein the copolymer is the copolymer ~~consists essentially of a polymer~~ of alanine, glutamic acid and lysine ~~in the molar ratio of about 5 parts alanine to 1.5 parts glutamic acid to 3.5 parts lysine~~.

~~19~~. A method for the treatment or prevention of experimental allergic encephalomyelitis, which comprises administering an effective amount of the composition of Claim ~~17~~ 1 by injection to a host suffering from or subject to the said disease.

20. The method of Claim 19, wherein the copolymer incorporated in said composition is selected from the group consisting of the copolymer ~~polymerizates of mixtures~~ of (1) alanine, glutamic acid, lysine and tyrosine in the molar ratio of about 6 parts alanine to 2 parts glutamic acid to 4.5 parts lysine to 1 part tyrosine; (2) alanine, aspartic acid, lysine and tyrosine in the molar ratio of about 5 parts alanine to 1.5 parts aspartic acid to 3.5 parts lysine to 1 part tyrosine; and (3) alanine, glutamic acid and lysine in the molar ratio of about 5 parts alanine to 1.5 parts glutamic acid to 3.5 parts lysine.

R E M A R K S

The specification has been amended and the claims revised as new Claims 11 to 20, inclusive, in an effort to obviate the rejections predicated upon Sections 101 and 112 (second paragraph) of the statute. New Claims 15-20 are readable on the previously elected species of the invention, Claims 15-18 being directed to applicants' therapeutic preparations per se and Claims 19

and 20 relating to the method for the treatment or prevention of experimental allergic encephalomyelitis with such preparations. The remaining claims, Claims 11-14, pertain to the copolymers which are the active ingredients of the preparations hereof and which the Examiner has previously held to constitute patentably distinct subject matter. Since, however, these claims have been limited to the particular copolymerizates found useful in applicants' therapeutic preparations and method for the treatment or prevention of experimental allergic encephalomyelitis, reconsideration and withdrawal of the restriction requirement, and examination of Claims 11-14 on their merits, together with the remaining claims, is again respectfully solicited.

The Examiner has questioned the disclosed utility of the invention, at least insofar as such relates to the treatment or prevention of multiple sclerosis. In order to obviate any further question, the specification has been amended herewith to indicate specific utility in the treatment or prevention of solely experimental allergic encephalomyelitis which disease, however, is a well known experimental model for multiple sclerosis and other autoimmune diseases. While specific utility is only claimed in connection with EAE, the preparations and method of treatment of the present invention may be of interest in the treatment of other autoimmune diseases.

The modified disclosure of utility is consistent with the laboratory studies which have heretofore been conducted and described in the literature by applicants or at their behest. In this connection and to complete the record, copies of the following papers relating to the subject matter of the present invention are attached as exhibits hereto:

Exhibit A - "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide", Teitelbaum, Meshorer, Hirshfeld, Arnon and Sela, Eur. J. Immunol. 1971, 1, pages 242-248;

Exhibit B - "Protection against Experimental Allergic Encephalomyelitis", Teitelbaum, Webb, Meshorer, Arnon and Sela, Nature, 240, No. 5383, pages 564-566 (1972);

Exhibit C - "Suppression by Several Synthetic Polypeptides of Experimental Allergic Encephalomyelitis Induced in Guinea Pigs and Rabbits with Bovine and Human Basic Encephalitogen", Teitelbaum, Webb, Meshorer, Arnon and Sela, Accepted for publication in the Eur. J. Immunol.

Exhibit D - "In Vivo and In Vitro Immunological Cross-Reactions between Basic Encephalitogen and Synthetic Basic Polypeptides Capable of Suppressing Experimental Allergic Encephalomyelitis", Webb, Teitelbaum, Arnon and Sela, Accepted for publication in the Eur. J. Immunol.

The attached papers document the utility of the compositions of the present invention for the treatment and prevention of experimental allergic encephalomyelitis and should, therefore, obviate any further question under 35 USC 101.

In regard to the rejection predicated upon the second paragraph of 35 USC 112, each of dependent Claims 16-20 depends, either directly or indirectly, from independent Claim 15. Accordingly, these claims are not subject to rejection as depending from claims drawn to the non-elected species. Secondly, the particular compounds which are polymerized to form the novel copolymers employed in accordance with applicant's invention are set forth in each of the claims, and the approximate molar ratios of the copolymers are defined in Claims 12-14, 16-18 and 20.

It is, however, respectfully submitted that the exact molar proportions need not be set forth in each of the application claims since, obviously, the specific proportions of the co-polymers prepared in applicant's experimental program may be modified without departing from the scope of their invention. Finally, each of the therapeutic preparations and method claims has been restricted to formulations for injectable administration, as suggested by the Examiner. In the light of the noted revisions and for the foregoing reasons, withdrawal of the indicated rejection is respectfully requested.

In regard to the further rejection based on the first paragraph of Section 112, it is submitted that the copolymers described may be prepared employing known syntheses, in the light of the teachings contained in the last paragraph on page 5 of the specification. In this regard, the Examiner is referred to Advan. Prot. Chem., 1958, 13, page 243, Katchalski and Sela, and to the further references noted in Section 2.3 of Exhibit A. The description in the specification is sufficient, when coupled with the noted references, to teach how to make the copolymers employed in applicant's invention.

Finally, the subject matter set forth in the claims as amended is neither anticipated by, nor obvious in view of, the disclosure of the cited Woodward patent. That reference relates rather to copolymers of L-leucine and phenyl-alanine, not to the particular copolymers recited in the present claims. Moreover, Woodward's copolymers are said to be useful as artificial fibers, resin constituents in paints, lacquers and other coatings, in plastic molding compositions and for like industrial purposes (Woodward patent, column 6, lines 38-61); there is neither disclosure nor suggestion that the Woodward copolymers would be useful in the treatment, or prevention, of experimental allergic encephalomyelitis.

In the light of the preceding amendments and for the above reasons, prompt and favorable reconsideration of the various grounds of rejection of the present application is respectfully solicited.

Respectfully submitted,

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EXHIBIT 8

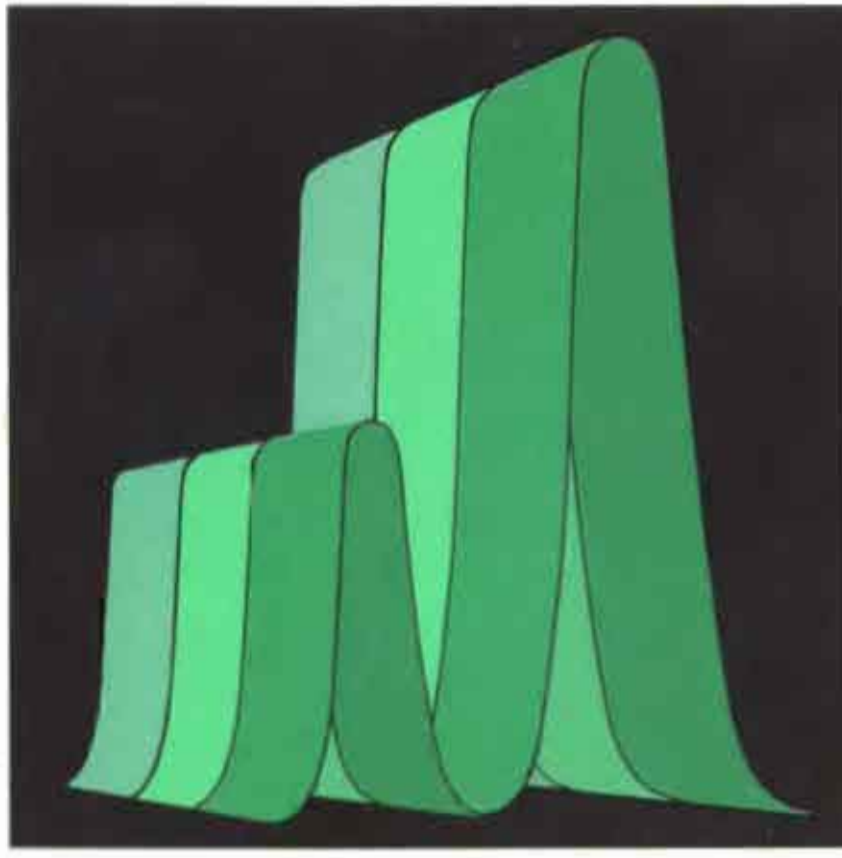
This exhibit is filed under seal
pursuant to the April 10, 2009 Protective Order

EXHIBIT 9

This exhibit is filed under seal
pursuant to the April 10, 2009 Protective Order

EXHIBIT 10

Gel filtration



Principles and Methods

6 th edition
18-1022-18

Pharmacia

Gel filtration
Theory and practice

ISBN 91-97-0490-2-6

Contents

Media	Pack size	Code No.
Sephadex G-25 Fine	100 g	17-0032-01
Sephadex G-25 Fine	500 g	17-0032-02
Sephadex G-25 Fine	5 kg	17-0032-03
Sephadex G-25 Medium	100 g	17-0033-01
Sephadex G-25 Medium	500 g	17-0033-02
Sephadex G-25 Medium	5 kg	17-0033-03
Sephadex G-25 Coarse	100 g	17-0034-01
Sephadex G-25 Coarse	500 g	17-0034-02
Sephadex G-25 Coarse	5 kg	17-0034-03
Sephadex G-25 Superfine	100 g	17-0031-01
Sephadex G-25 Superfine	5 kg	17-0031-03
Sephadex G-50 Fine	100 g	17-0042-01
Sephadex G-50 Fine	500 g	17-0042-02
Sephadex G-50 Fine	5 kg	17-0042-03
Sephadex G-50 Medium	100 g	17-0043-01
Sephadex G-50 Medium	500 g	17-0043-02
Sephadex G-50 Medium	5 kg	17-0043-03
Sephadex G-50 Coarse	100 g	17-0044-01
Sephadex G-50 Coarse	500 g	17-0044-02
Sephadex G-50 Coarse	5 kg	17-0044-03
Sephadex G-50 Superfine	100 g	17-0041-01
Sephadex G-50 Superfine	5 kg	17-0041-03
Sephadex G-75	100 g	17-0050-01
Sephadex G-75	500 g	17-0050-02
Sephadex G-75	5 kg	17-0050-03
Sephadex G-75 Superfine	100 g	17-0051-01
Sephadex G-75 Superfine	5 kg	17-0051-03
Sephadex G-100	100 g	17-0060-01
Sephadex G-100	500 g	17-0060-02
Sephadex G-100	5 kg	17-0060-03
Sephadex G-100 Superfine	100 g	17-0061-01
Sephadex G-100 Superfine	5 kg	17-0061-03

Media	Pack size	Code No.
Sephadex G-150	100 g	17-0070-01
Sephadex G-150	500 g	17-0070-02
Sephadex G-150	5 kg	17-0070-03
Sephadex G-150 Superfine	100 g	17-0071-01
Sephadex G-150 Superfine	5 kg	17-0071-03
Sephadex G-200	100 g	17-0080-01
Sephadex G-200	500 g	17-0080-02
Sephadex G-200	5 kg	17-0080-03
Sephadex G-200 Superfine	100 g	17-0081-01
Sephadex G-200 Superfine	5 kg	17-0081-03
Sephadex G-25 DNA Grade SF	25 g 100 g	17-0572-01 17-0572-02
Sepbadex G-50 DNA Grade F	25 g 100 g	17-0573-01 17-0573-02
Sephadex G-100 DNA Grade M	25 g 100 g	17-0045-01 17-0045-02
Sephadex G-100 DNA Grade SF	25 g 100 g	17-0574-01 17-0574-02
Handbook, Gel Filtration, Theory and Pracitce		18-1022-18

Standards	Pack size	Code No.
Gel Filtration LMW Calibration kit	1 kit	17-0442-01
Gel Filtration HMW Calibration kit	1 kit	17-0441-01
Blue Dextran 2000	10 g	17-0360-01

Contents of the gel filtration calibration kits.

Low Molecular Weight Gel Filtration Calibration Kit			
Protein	M Weight	Stokes' Radius Å	Source
ribonuclease A	13 700	16.4	bovine pancreas
chymotrypsinogen A	25 000	20.9	bovine pancreas
ovalbumin	43 000	30.5	hen egg
albumin	67 000	35.5	bovine serum
Blue Dextran 2000			

High Molecular Weight Gel Filtration Calibration Kit			
Aldolase*	158 000	48.1	rabbit muscle
catalase	232 000	52.2	bovine liver
ferritin*	440 000	61.0	horse spleen
thyroglobulin	669 000	85.0	bovine thyroid
Blue Dextran 2000			

Each Kit contains 50 mg of each protein and 50 mg of Blue Dextran 2000.

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EXHIBIT 11

This exhibit is filed under seal
pursuant to the April 10, 2009 Protective Order